REMARKS/ARGUMENTS

Claims 28-30 and 52-69 are presently pending, upon entry of the amendments herein. Applicant respectfully requests that previously canceled claims 34-51 (deleted in their entirety for the reasons of record) are reinstated as new claims 52-69 by this amendment. M.P.E.P. § 608.01(s). No new matter is being entered by entry of these amendments.

I. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 28-30 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Applicants respectfully request reconsideration of this rejection, as there is no evidence of record indicating that those skilled in the art would be unable to practice the methods ***as they are claimed.***

Claims 28-30 are directed to methods for treating an organism having a disease characterized by the undesired production of a protein [the preamble], comprising ***contacting said organism*** [the method step]. Notably, the claims are not drawn to "curing" or to "eradicating a disease state." Instead, a lower threshold of "treating" is addressed. "Treating" requires only the administration of a compound to an organism to satisfy the claimed "contacting" step. *See also*, Webster's II defines the verb "treat" as follows: "to subject to an action, process or change."

Given that claims 28-30 require only a minimum of "contacting" and not, for example, "curing", the only issue under 35 U.S.C. §112 is whether those skilled in the art having knowledge of Applicants' disclosure would require "undue experimentation" in performing the claimed step of "contacting." Enablement may be provided by "illustrative examples," *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993), and the initial burden is

on the PTO to demonstrate an objective factual basis for questioning Applicants' disclosure. *Id.* However, the inquiry cannot stray from the metes and bounds of the claim language itself. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Pat. Off. Bd. App. 1987) (the invention that must be enabled is that defined by the claims).

Significantly, the outstanding Office Action does not appear to assert that those skilled in the art would need to engage in undue experimentation to contact an organism with one of the claimed compounds. Instead, the rejection appears to be resurrecting a stringent notion of therapeutic utility that was unambiguously rejected by the PTO many years ago, see M.P.E.P. § 2107.02; *In re Sichert*, 566 F.2d 1154 (C.C.P.A. 1977).

The Examiner's improper imposition of an enablement threshold exceeding what is required to support the pending claims is demonstrated by the following:

- "As stated in previous Office actions, the state of the prior art is such that ***the efficacy of antisense oligos in vivo varies unpredictably from their efficacy in vitro, such that one cannot predict a priori which will work in vivo and which won't.*** (Office Action page 5 lines 22-24, emphasis added).

- The Examiner continues to rely on references that purportedly "demonstrate the unpredictability of antisense-mediated ***therapy"*** (Id. at page 6 lines 1-2, emphasis added) .

- Based on these references, the Examiner concluded that "the field of antisense related ***therapy*** [is] unpredictable . . . ." (Id. at page 6 line 10, emphasis added).

- The instant enablement rejection focused specifically on why predicting in vivo antisense ***efficacy*** from in vitro data is unpredictable." (Id. at page 7 lines 8-9, emphasis added).

- ". . . the real issue at hand, that is, inherent problems in ***predicting in vivo efficacy*** of antisense compounds based on in vitro inhibition data." (Id. at page 7 lines 11-12, emphasis added).

- ". . . only one antisense drug has ever been shown to have ***therapeutic value*** . . . "(Id. at page 8 lines 1-2, emphasis added).

- "Applicants' piecemeal breakdown of the examiner cited references are not convincing, because they fail to indicate where in these review articles it is shown that art of antisense ***therapeutics*** is in any way predictable." (Id. at page 8 lines 2-5, emphasis added).

- None of the applicants' supplied references provide a meaningful blueprint for resolving the known obstacles in the art in using data obtained *in vitro* to predict *in vivo* ***therapeutic success*** . . . ." (Id. at page 10 lines 15-17, emphasis added).

As noted above, the claims are not drawn to any particular level of efficacy or to achieving a successful therapeutic cure. The claims are drawn only to "treating" by "contacting an organism" with an oligonucleotide. Hence the Examiner's extensive argumentation regarding efficacy and therapeutic success, quoted above, is simply inapposite.

Moreover, the Examiner's new support for maintaining the enablement rejection – the recently reported Phase III clinical trial results of the Affinitak™ in combination with carboplatin and paclitaxel -- is factually inaccurate.

The Examiner characterizes the trial as a "failure" (Office Action at page 11 line 6), presumably based on that portion of the Reuters article that reported the overall median patient survival rate, i.e., patients receiving Affinitak™ plus the chemotherapy regimen of carboplatin and paclitaxel experienced a median survival of 10 months, compared to 9.7 months for patients receiving the chemotherapy regimen alone (*Id.*). However the Reuters article also reported that in the sub-set of 256 patients who completed the prescribed course of chemotherapy, *i.e.*, patients receiving the prescribed number of doses of Affinitak™ plus the chemotherapy regimen, the Affinitak™ plus the chemotherapy regimen showed a median survival of 17.4 months versus 14.3 months for patients receiving only the chemotherapy

regimen ($p = 0.054$). This sub-set of data is fully supportive of applicants "treating" claim language.

While the Affinitak™ trial did not meet the primary endpoint for FDA approval purposes, there is no indication in the Reuters article that this antisense drug fails to exert an effect in clinical subjects. Indeed, Attinitak™ only reached the stage of Phase III clinical trial "failure" (i.e., failure to meet a predesignated statistical endpoint in a large population of patients, in a multidrug treatment protocol) by first having demonstrated earlier Phase I safety and Phase II clinical effects in clinical subjects. Irrespective of not meeting the primary endpoint of the trial for FDA approval, together the Phase III sub-set data and the Phase I and Phase II data rebut that questioned by the Examiner – that is whether an antisense nucleotide can be delivered in an animal such that the oligonucleotide are "crossing cell membranes, avoiding non-specific binding with cellular proteins, overcoming target secondary structures and bound transcription factors, and finally inhibiting the expression of the gene." (Office Action at page 8 lines 20-22).

More fundamentally, the Examiner's apparent desire to see clinical data establishing "efficacy" or "therapeutic value" for patentability of an antisense drugs simply does not take into account the realities of drug development. While it might be the ultimate goal of the clinician to achieve marketing approval based upon on single Phase III pivotal clinical trial, it is a reality of the clinical trial process that predetermined end points are often not met. "Failure" of the first Phase III clinical trial does not necessary mandate that marketing approval is not obtainable. Indeed many drugs ultimately get marketing approval having failed their first Phase III clinical trial. Valuable information can be gained from a failed clinical trial that can then be then used to design a more successful follow-up second clinical

trial. Subsequent Phase III trials have ultimately lead to FDA marketing approval of many other drugs. Achieving a particular therapeutic endpoint in a clinical trial (in Affinitak's case, a substantial increase in survival time in a very sick patient population taking multiple drugs) requires optimal dosing levels for that *particular* statistical endpoint. Achieving increased survival time requires not only that the target selected for drug action be causally related to the result, but that it act without countervailing influences from other physiological targets or disease-related events. Given these variables, it is not surprising that in a complex disease such as cancer the vast majority of drugs do not achieve FDA "success" on the initial Phase III clinical trial. Nonetheless, such drugs are patentable. *In re Brana*, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995).

When Applicants' specification is reviewed for support for claimed methods that involve simply "contacting an organism" rather than affecting a cure, one finds more than ample illustrative examples to meet the enablement standard of *In re Wright, supra.* The specification describes administration at, e.g., page 43 line 9 through page 44 line 33, and at page 46 line 31 through page 47 line 4. The specification also provides substantial exemplary detail regarding particular embodiments such as antisense to protein kinase C (36:28-37:15 and 39:11-15), cell adhesion molecules ICAM-1, VCAM-1 and PCAM-7 (37:16-38:22), RAS (38:23-39:10) and JNK (39:15-40:23). The Examiner will note that these sections provide numerous references to US patents and patent applications, all of which are incorporated by reference, and each of which provides additional teaching regarding administration of particular antisense oligonucleotides. Finally, Example 4 describes administration of exemplary claimed oligonucleotides to rats via intravenous administration.

Given a proper comparison of the claim language to the teaching of the specification, Applicants submit that the pending claims are fully enabled, and request that the Examiner withdraw his rejections under 35 U.S.C. section 112.

Conclusions:

Applicant requests the Examiner to:

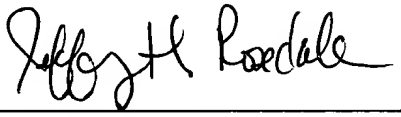
(1) add claims 52-69;

(2) reconsider and withdraw the rejection of the claims; and

(3) pass claims 28-30 and 52-69 to allowance.

If the Examiner is of contrary view, the Examiner is requested to contact the undersigned attorney at 215-568-3100.

Date: July 23, 2003



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